Combined hormonal contraceptives
CHC Session II

How to take a detailed risk history / understanding VTE and ATE risk balance risks / benefits

Advanced slide kit complementing the WHO training tool www.fptraining.org

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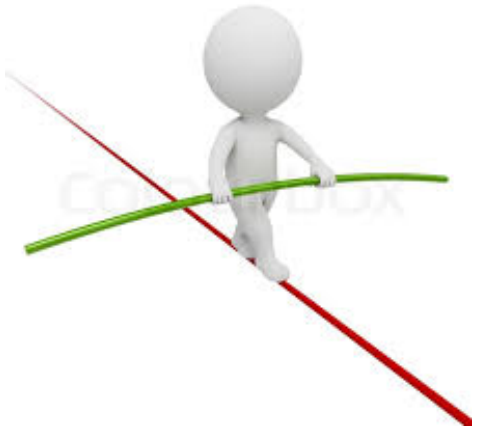
Contents

- How to take a history before contraceptive counseling
- Special risk screening for use of CHCs (higher risks/ lower risks and WHO MEC category 4 criteria criteria)
- There are two types of risks one affecting the arterial system and one the venous system
- **VTE risk in healthy young women without contraception and in pregnancy**
  - EMAS recommendation: VTE risk according to progestin type and method of application
  - VTE risk according to estrogen dose and type of estrogen
  - Understand what is meant by a positive family history and what it means for risk counselling
  - VTE risk in women with thrombophilia
  - Overview risk for VTE in numbers and multiplication of risks
  - VTE risk with age, obesity and duration of CHC use
- **Arterial risk**: stroke and myocardial infarction in numbers, in relation to age and obesity
- Balancing risks against other contraceptive options and benefits during counselling

Balancing risks and benefits



- This session discusses a lot of potential risks associated with use of CHC
- Only a subgroup of women who will experience complications with CHC use
- CHCs are not dangerous for healthy young women

Taking a history before contraceptive counseling

General History

Gynaecologic history

Reproductive health goals

Personal situation

General history

Most important aspects to avoid severe complications

General history

Exclude:

1. Previous venous blood clot (venous thrombosis), stroke or heart attack
2. Thrombogenic mutations
3. Migraine with aura
4. Hypertension (≥160/ ≥100mm Hg)
5. Severe liver or gall bladder disease
6. Systemic lupus erythematodes
7. Diabetes with vascular complications
8. Smoking and age >35 years
9. A venous blood clot, stroke or heart attack in any first degree relative aged ≤ 50 years

www.fptraining.org : Provides further detailed information

General history

Further issues important to address before balancing risks and benefits

General history

1. Medical conditions
2. Surgery
3. Medication (include phytotherapeuticals): consider potential interactions
4. Psychic disorders and eating disorders
5. Alcohol, drugs and allergies
6. Smoking and weight

www.fptraining.org: Provides further detailed information

Gynaecological history

The most important aspects to optimise counselling and use benefits of CHC

Gynaecological History

1. Menstrual cycle: Interval, duration, intensity of bleeding, symptoms and date of last menstruation
2. Pregnancies: births, abortions, breastfeeding
3. Breast, cervical, ovarian and endometrial cancer
4. Ovarian cysts
5. Previous contraceptive methods : tolerability and adherence
6. Previous use of emergency contraception

Personal situation and reproductive health goals

Reproductive health goals

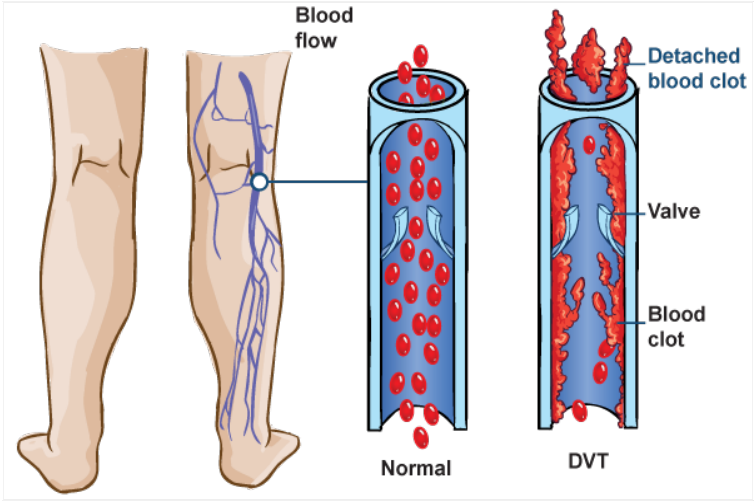
1. Duration of relationship with partner
2. Plans for motherhood
3. Need for long-term contraception
4. Financial issues
5. Wish for permanent contraception
6. STI protection

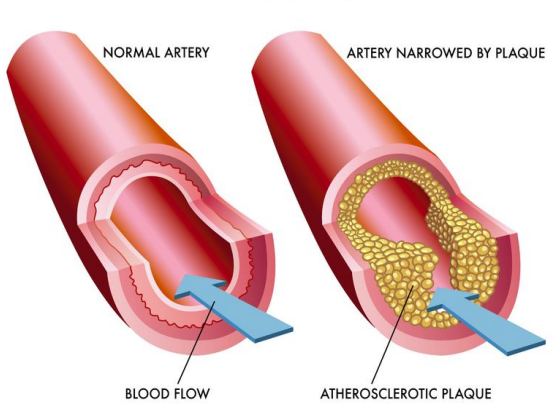
More detailled cardiovascular risk screening for use of CHC

- History of venous thromboembolism (VTE), pulmonary embolism, myocardial infarction (MI) or stroke: **WHO MEC category 4**
- Known thrombophilia: **WHO MEC category 4**
- Migraine with aura: **WHO MEC category 4**
- Hypertension ≥160/≥100 mmHg: **WHO MEC category 4**
- Positive family history of VTE, pulmonary embolism, MI, stroke: **Strong contraindication**
- Obesity
- Age >35 years
- Smoking
- Migraine without aura
- Multiplicative effect of less strong risk factors (smoking and age)

Differentiate arterial from venous risks

- **VTE** in CHC users is an acute event which results from the effects of hormones on the coagulation system.
- VTE typically affect younger users and newstarters.
- **Arterial** events typically occur when the arteries are already damaged by atherosclerosis and a thrombus develops on the plaques potentially promoted from the effects of CHC on coagulation.
- Age >35 and any condition related to atherosclerosis are important risk factors





1. VTE and deep venous thrombosis (DVT)

Risks, in numbers, according to :

- Type of CHC
- Type of risk factor

VTE risk in healthy young women not using CHC

Risk of developing a VTE in a year

	Incidence	Relative risk
1. Healthy young women	2-3/10000	1
2. Pregnancy	48-60/10000	12
3. Healthy user of CHC	5-12/10000	2-4

CHC use in healthy women is associated with a two-fourfold VTE risk.

Risk with different types of pills

Statement of the European Medical Agency 2013

Risk of developing a blood clot (VTE) in a year

Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a CHC containing **levonorgestrel, norethisterone** or **norgestimate**	About 5-7 out of 10,000 women
Women using a CHC containing **etonogestrel** or **norelgestromin**	About 6-12 out of 10,000 women
Women using a CHC containing **drospirenone, gestodene** or **desogestrel**	About 9-12 out of 10,000 women
Women using a CHC containing **chlormadinone, dienogest** or **nomegestrol**	Not yet known*

* More information next slide

www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000581.jsp&mid=WC0b01ac05806b6b24

Ref 1

VTE risk and progestin type in CHCs

CHC with third and fourth generation progestins are associated with the **twofold higher VTE** risk in comparison with those containing a second generation progestin.

Consequences for prescription of CHCs

- CHCs with third and fourth generation progestins are associated with a twofold higher risk of VTE in comparison with CHCs containing levonorgestrel
- The differences in VTE risks between CHC with different progestins are low (odds ratio 2). In numbers these are 3-5 events in 10000 women/year.
- It is recommended to start women on a product containing a second generation progestin (levonorgestrel), if there is no reason to prescribe a CHC associated with a slightly higher VTE risk.
- Regular reassesment of risk factors is needed

VTE and estrogen type and dosage

- No difference in VTE risk was found between pills containing 20 µg or 30 µg ethinylestradiol
- CHC with estradiol or estradiol-valerate are not associated with a higher risk for VTE in comparison with third generation CHCs; The VTE risk is not lower or equal to second generation pills (EE/LNG).

Ref 1,2

Risk factors for VTE

a. A Family history (1st degree relative < 50 years)
b. Thrombophilia
c. Obesity
d. Age ? → Risk is more on the arterial slide
e. Smoking ? → Risk is more on the arterial slide

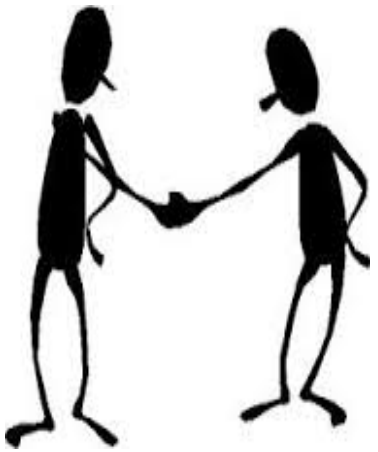
Consider the multiplicative effect of risk factors

Risk factors for VTE

a. Family history (1st degree relative < 50 years)

Positive family history Definition

- A family history for VTE is positive, if a first-degree relative has experienced a VTE
- There is no general agreement about the age of this first-degree relative.
- Age < 50 years is typically used in haematological studies



In the context of CHC use it makes sense to limit the age of the first-degree relative to 50 years, however in some situations additional aspects have to be considered

Ref 1-4

Positive family history
How high is the VTE risk in non- CHC users?

Family history	VTE-Risk odds ratio (1)
negative	1
positive any relative	2.2
positive relative < 50 years	2.9
> 1 relative	2.9
2 relatives, one <50 years	4

Relation to proband	VTE-Risk odds ratio (2)
Sibling	2.5
Son/daughter	2.6
Parent	2.1
Second degree relative	1.5-2.3
2 relatives, one <50 years	4

Note, that age of the first degree relative < 50 or not does not make such a difference!

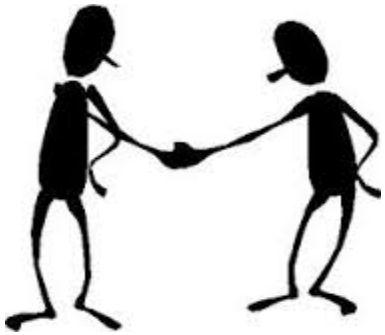
Adapted from Ref 1,2

Positive family history
Probable risk for CHC users

- The VTE risk with a first-degree relative is two- to threefold
- The risk with additional use of CHC is 15 fold
- CHC should rather not be prescribed in such a situation, Progestin-only methods and Intrauterine devices can be used.

Ref 1

Medical condition
Positive Family history



<u>Efficient and safe options for contraception</u>

- Copper IUD and LNG-IUS
- POP Desogestrel
- Implant
- DMPA
- Permanent methods

Should women with positive family history be screened for hereditary thrombophilia? NO

- 29.7 % of women with family history (1st degree relative) and VTE are diagnosed with thrombophilia (genetic risk)
- The classical five thrombophilias are not a typical cause for a positive family history.
- A positive FH is the stronger predictor for VTE than cost-intensive thrombophilia screening
- Testing women with positive FH may give wrong reassurance if the patient is tested negative. She nevertheless will have a markedly increased risk of CHC-related VTE compared with the general population.
  CHCs therefore should not be prescribed.

Ref 1

Risk factors for VTE

b. Thrombophilia

Hereditary thrombophilia

Incidence and VTE risk without CHC (heterozygous carriers)

	Prevalence	Risk for VTE
• Protein C deficiency	0.1%	10 fold
• Protein S deficiency	0.1%	10 fold
• Antithrombin III deficiency	0.1%	10 fold
• Prothrombin 20210 A Mutation	2-3%	3-8 fold
• Factor V Leiden	5-10%	3-8 fold

Adapted from Ref 1

Severe hereditary thrombophilia

Incidence and VTE risk in CHC users

Type of thrombophilia	Incidence / 10000 woman years CHC users	Incidence / 10000 woman years Non CHC users (all are relatives and thus have a positive family history and a higher baseline risk in comparison to young healthy women)
Severe Antithrombin deficiency , Protein C deficiency, Protein S deficiency	430-462	48-70
Mild Factor V Leiden, Prothrombin 20210 A Mutation	49-200	19

Adapted from Ref 1,2

Hereditary thrombophilia
Recommendation for CHC use

- Based on the high additive risk for VTE CHC-use should be **avoided** in asymptomatic women with severe thrombophilia

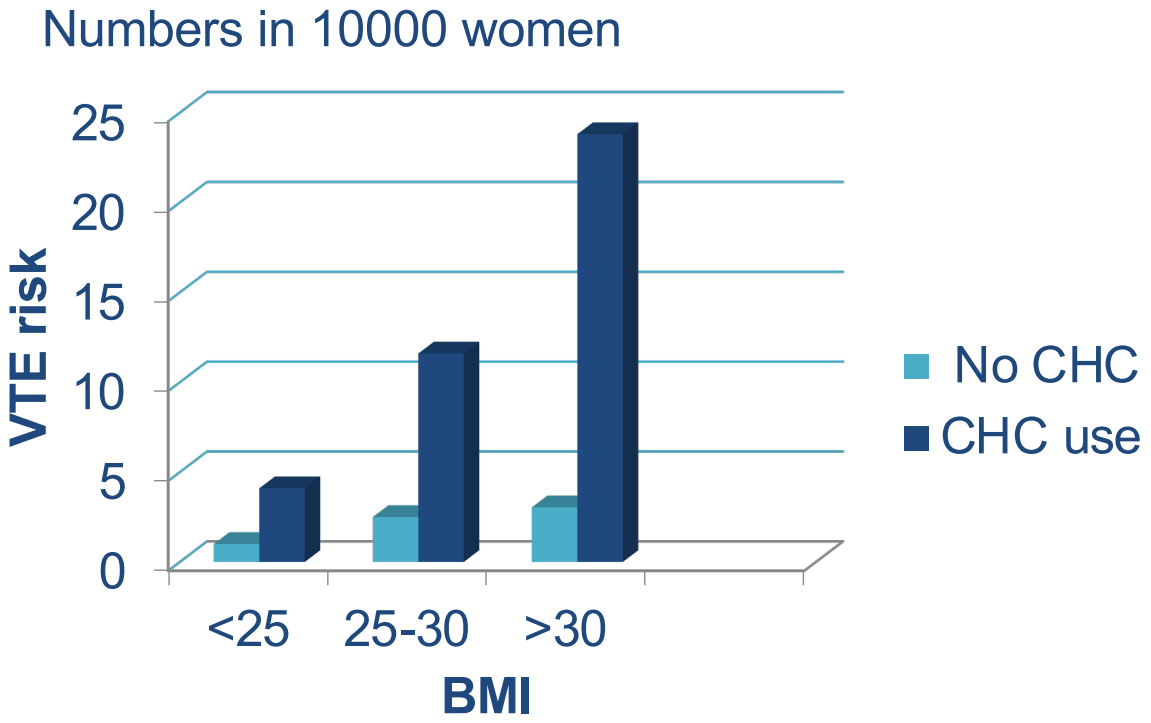
- Testing women with positive family history may give wrong reassurance if the patient is tested negative. She nevertheless will have a markedly increased risk of CHC-related VTE compared with the general population.

Adapted from Ref 1

Risk factors for VTE

c. Obesity

VTE and Obesity



Obesity increases the risk for VTE 2-3 fold.
The risk strongly increases with CHC use and can multiply with other risks like age. The degree of obesity has an impact as well.

Ref 1-3

Risk factors for VTE

d. *Age ? → Risk is more on the arterial slide*

e. *Smoking ? → Risk is more on the arterial slide*

VTE risk
Age and smoking

Smoking as risk factor for VTE is discussed controversial, in heavy smokers some studies indicate an increased risk HR 1.5.

Age is not important as risk factor for VTE in women from age 35 onwards. For younger women other additional risk factors, like obesity have to be excluded.

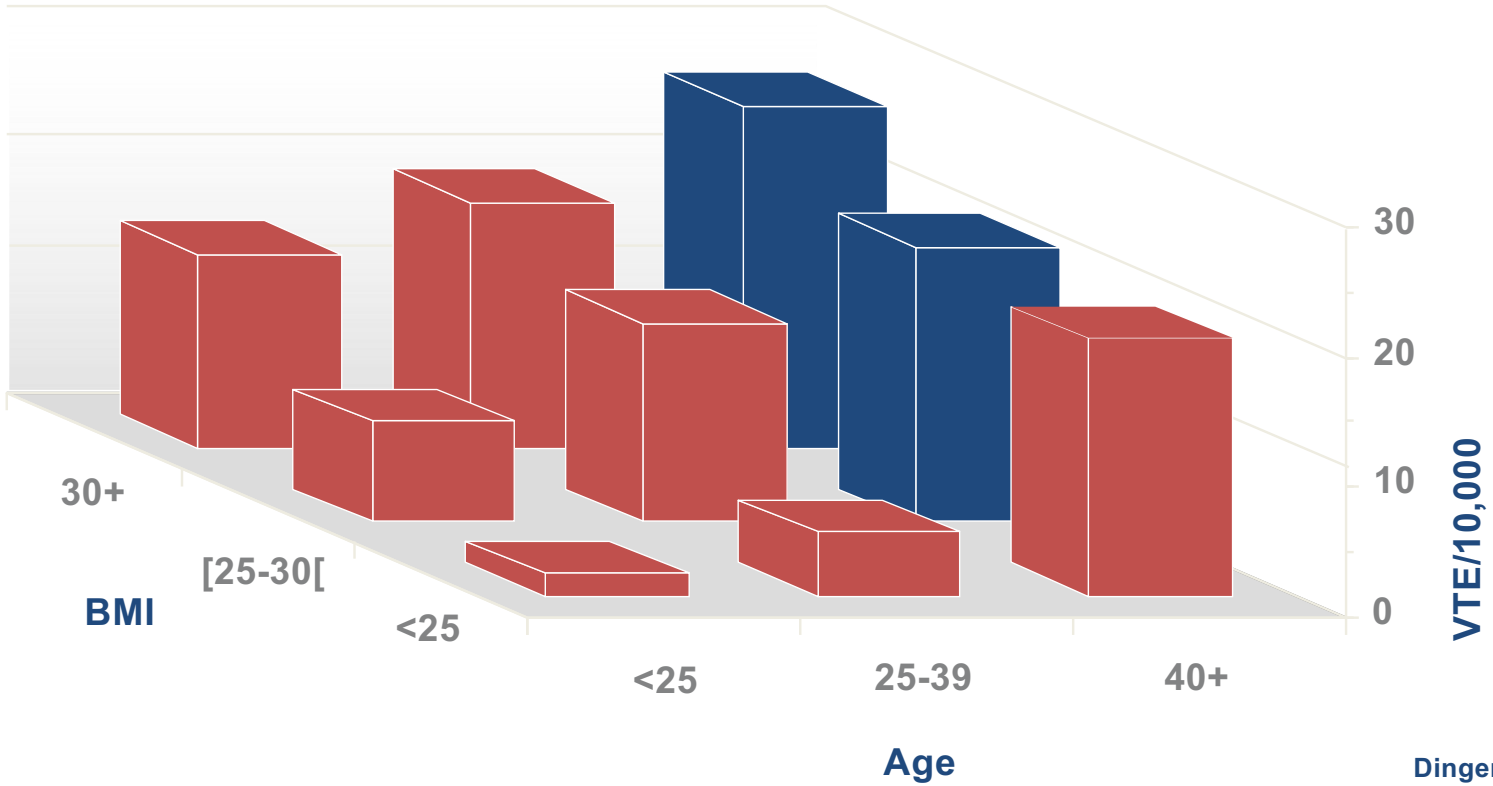
Incidence in non-CHC users:

Incidence age 20-24	2.7/10000
Incidence age 35-39	3.9/10000

Ref 1,2

Multiplication of risk factors

Increasing impact of age and BMI on VTE risk in COC users*



Dinger, EURAS Study

* Risk estimates based on 115 VTEs in 116,708 WY of exposure

Ref 1,2

VTE risk
Age and smoking

- ***Age and smoking are not strong as single risk factors for VTE in fertile women.***
- ***However, take into account the multiplicative effect of less strong risk factors and consider the arterial risk as well.***

Ref 1,2

Risk of cerebral venous thrombosis (CVT)

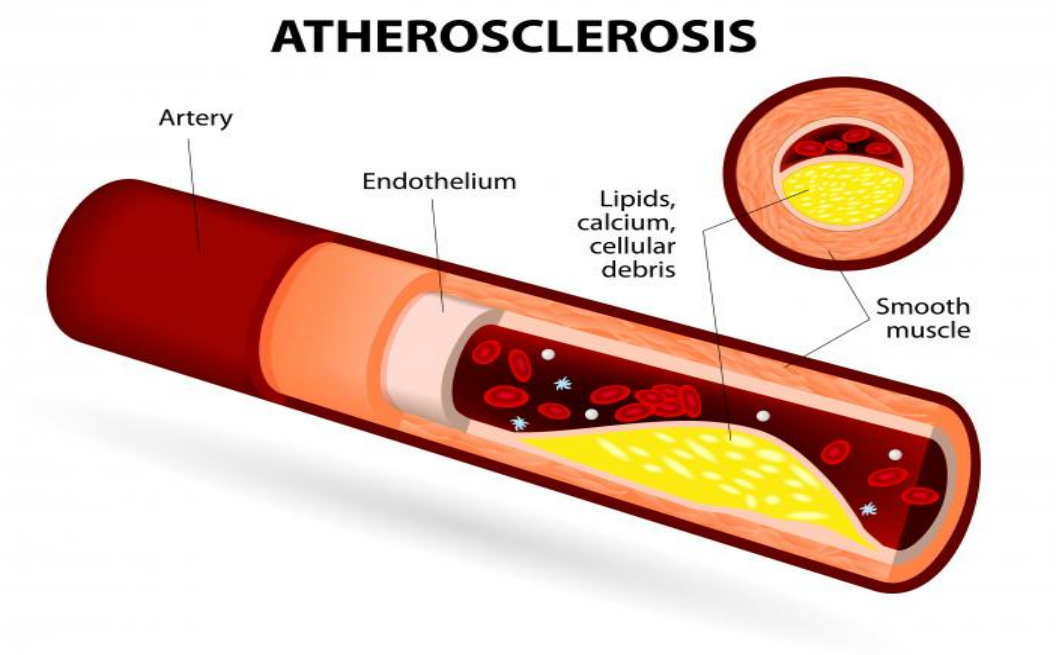
- CVT incidence among adults 0.13/10000 years
- Women and persons younger than 50 years are at greater risk
- Risk factors: hereditary thombophilia, CHC use, anaemia, trauma
- Typical symptoms include: headache, papiloedema, epileptic seizure

The OR for CVT risk in CHC users is 5.5, but the risk is very small, as baseline incidence is low

Ref 1

2. ATE risks in numbers

Myocardial infarction and ischemic stroke



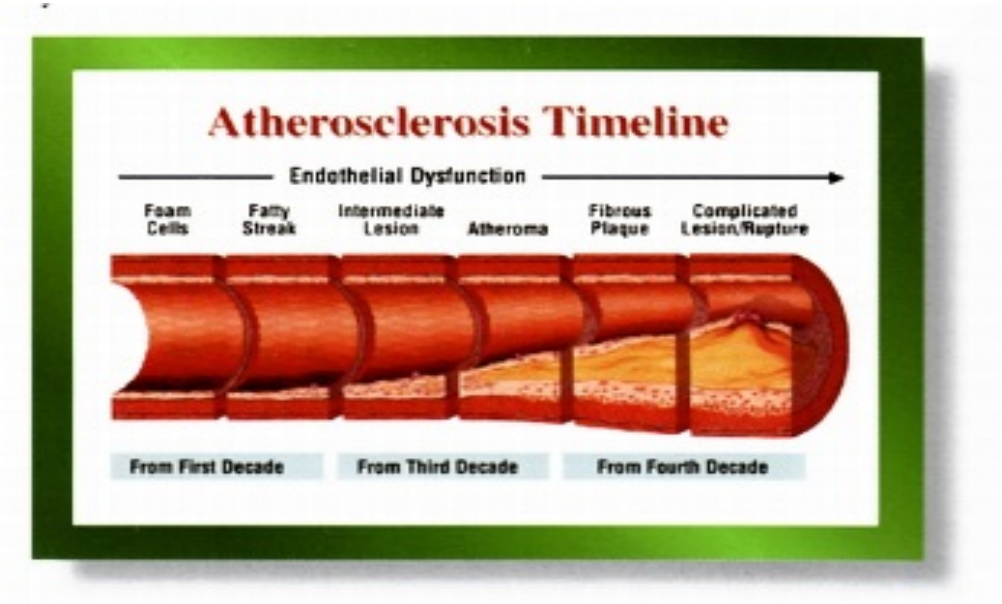
Arterial events

Myocardial infarction and thrombotic stroke in CHC users – Important risk factors

- Age >35 years
- Obesity
- Migraine with/without aura
- Smoking
- Hypertension
- Diabetes
- Dyslipidaemia
- Family history

Myocardial infarction

The development of atherosclerotic plaques progresses over the years. Therefore such age and longlasting risk factors over the years are important for the individual risk.



When balancing risks it has to be considered that MI is associated with a much higher mortality in comparison to VTE. However, MI is rare in young women. Special risk factors for atherosclerosis are high blood pressure, smoking, diabetes and hyperlipidemia

Age-related incidence of MI in none-CHC users

Incidence per 100 000 women per year / 2 independent studies 1999 and 2012		
	Age 20-24	Age 40-44
Myocardial infarction (1)	0.2	30 ←
Myocardial infarction (2)	0.7	25.4 ←

- Age has a major impact on risk for MI. This risk increases strongly if other risk factors like smoking, obesity or hypertension or dyslipidemia.
- Check carefully for risk factors if you prescribe CHC in women aged > 35 years
- Discuss contraceptive options without risk (POP; IUD; permanent methods)

Ref 1,2

Ischemic stroke in CHC users Role of pill type

- Use of low-dose CHC is associated with a **twofold** risk for ischemic stroke
- Risk for ischemic stroke in CHC is the same with all types of progestins
- Progestin-only pills are not associated with an increase of risk

Ref 1,2

Multiplicative influence of age, smoking and CHC use on incidence of MI infarction

Incidence per 1 000000 woman-years	**Age < 35**	**Age > 35**
No pill, no smoking	0.8	10
Pill use, no smoking	4	40
No pill, smoking	8	88
Pill use and smoking	43	485

Ref 1

Migraine and stroke with CHC use Multiplication of risks

	Odds Ratio
All migraine	2.3 - 3.7
Migraine without aura	2.3 – 3.8
Migraine with Aura	3.8 – 8.6
Migraine und COC	5 – 17
Migraine and smoking	10.2
Migraine, Smoking and COC	34.4

Migraine with aura and use of CHC are associated with a considerable increase in risk for ischemic stroke. This risk already exists in young women.

Ref 1-3

Arterial events

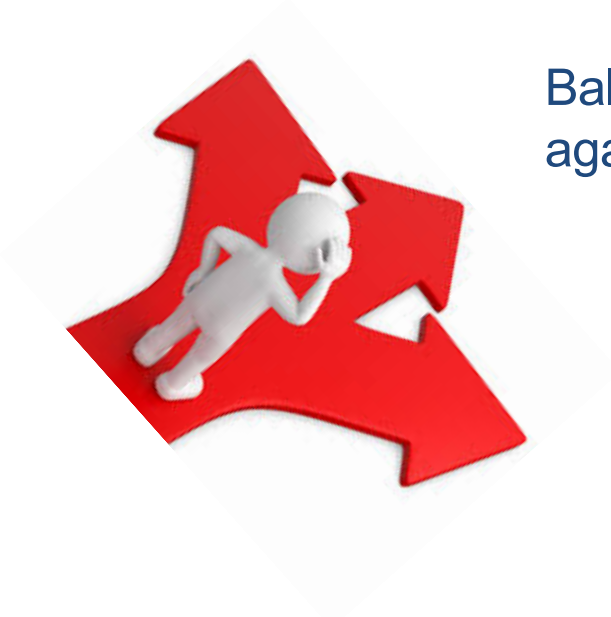
Counselling under consideration of age

	Age < 35 years	Age >35 years	Age >35 MEC if available for this situation
Obesity	Possible	better not, consider DVT risk	
Migraine with aura	no	no	4
Migraine without aura	possible	no	3
Hypertension	Possible if BP140-159/90-99	no	4
Smoking	possible	no	4
Diabetes	possible if no vascular complication	no	4
Dyslipidemia	possible	no	4

Contraception in women with cardiovascular risk factors

Take time to collect all important information

Effective estrogen-free method would be best



Balance less effective method against the risk of pregnancy

In very difficult situations where the danger of pregnancy is high and no other option is applicable or available, consider prescribing CHCs despite the risk